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What Is the Structural Substrate for Atrial Fibrillation?

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Atrial fibrillation (AF) is the most prevalent sustained form of cardiac arrhythmia and its incidence is on the increase worldwide [1]. It is a major cause of ischemic stroke, accounting for up to 15% of all cases [2], and typically entails a significant loss of quality of life [3]. Age is the major risk factor for the development of AF, but its epidemiology is varied and includes other risk factors such as hypertension, heart failure, myocardial infarction, and postoperative complications [4].

The traditional therapeutic approach to AF is drug treatment, with rhythm control and rate control as two separate treatment strategies [5]. In rhythm control, the goal is to restore sinus rhythm using class IA, IC or III drugs. While sinus rhythm is clearly the most desirable rhythm, it can currently be achieved only with drugs that potentially cause arrhythmias in the ventricles [6]. Rate control, on the other hand, is aimed at adjusting the ventricular activation rate while leaving the atria fibrillating. Rate control avoids most of the ventricular arrhythmias that rhythm control suffers from, but it allows atrial remodeling to progress and increases the risk of secondary stroke [7].

About 15 years ago, it was shown that AF induces changes in atrial tissue in a way that promotes the initiation and sustenance of AF [8, 9]. Since then, the question of which tissue properties promote AF has been a focus of arrhythmia research. The action potential duration decreases significantly during AF, which is caused by a reduction in $I_{Ca,L}$ density [10]. While the potassium currents I_{to} and I_{K1} are also reduced [11], the net result is still a shortening of the action potential. This shorter action potential facilitates the induction of AF ('AF begets AF' [8]). Loss of cell coupling also promotes AF. Various animal model studies of AF have failed to produce consistent findings in the changes in the expression levels of connexin-43 (Cx43) and connexin-40 (Cx40), but one consistent observation is a heterogeneous loss of connexin function [12, 13]. Gap junction heterogeneity may also result from mutational alterations of connexin function rather than protein distribution [14, 15]. While no changes in conduction velocity have been observed, microheterogeneities in conduction may contribute to AF initiation and maintenance. Finally, fibrosis promotes AF [16]. Fibrosis is often caused by congestive heart failure, and this may explain why congestive heart failure is a risk factor for AF [17]. Fibrosis is also promoted by the atrial dilation associated with AF itself, providing another feedback mechanism for the perpetuation of AF.

The question of what substrates promote AF has become particularly important with the rise of ablation as a therapy. A decade ago, it was first shown that episodes of paroxysmal AF most often originate in the pulmonary

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vein region, and that electrical isolation of the pulmonary veins via ablation restores sinus rhythm in most patients with paroxysmal AF [18]. Subsequent studies confirmed these findings, but also showed that AF recurs over time in a significant part of the patients. Consequently, much effort has been spent in improving ablation strategies, particularly in identifying the most effective ablation targets.

One emerging ablation target are those locations in the atria that exhibit complex fractionated atrial electrograms (CFAEs). The relationship between local atrial electrograms and corresponding wave behavior was first studied by Konings et al. [19], who found that CFAEs typically occur in areas of slow conduction and/or at pivot points where the wavelets turn around at the end of the areas of functional blocks. Subsequently, it was shown that ablation of CFAE regions can be very effective in terminating AF [20]. A recent study comparing current ablation strategies concludes that ablating the CFAE regions combined with the isolation of the pulmonary veins is significantly superior to just isolating the pulmonary veins alone [21].

In the current issue of *Cardiology*, Liu et al. [22] investigate the structural substrate underlying the genesis of CFAEs. The authors employ endocardial extracellular mapping techniques to identify the site of acute AF induction and subsequent microscopic analysis of these sites for collagen fibrosis and disruption of Cx43 gap junction distribution. Sustained AF was acutely induced in twelve young adult pigs by continuous infusion of acetylcholine and right atrial pacing. The sites of left CFAEs were determined using a saline-irrigated radiofrequency catheter. CFAE and non-CFAE sites were marked by triangular radiofrequency ablation of surrounding sites and then subjected to histological and immunohistological analysis of fibrotic area and Cx43 gap junction content.

The findings are, in short, that at sites showing CFAE, fibrosis is enhanced and Cx43 expression is reduced. The conclusion is that fibrosis and lack of Cx43 are the cause of CFAEs. This is an important piece in the puzzle of AF because it explains a promising predictor of ablation success in terms of tissue structure. It is encouraging to see that a mechanistic understanding of AF maintenance is getting nearer. At the same time, the results presented should encourage research to resolve important related questions, such as whether there is a relationship between the occurrence of CFAEs and Cx40 expression (Cx40 is about as abundant in the atria as Cx43).

The wealth of results on AF in the past decade has already led to dramatic improvements in its therapy. One approach for further progress is to establish the structural substrates of AF and optimize strategies to neutralize them. Another important possibility is the development of new drugs, such as drugs targeting atrium-specific ion channels to re-establish sinus rhythm. If both approaches are pursued vigorously, there is good reason to hope that AF therapy will continue to improve in the years ahead.

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